STIC Search Report
EIC 1700

USPTO

STIC Database Tracking Number: 178934

TO: Ben Sackey
Location: REM 5C18
Art Unit : 1626
February 10, 2006

Case Serial Number: 10/697545

From: Kathleen Fuller
Location: EIC 1700
REMSEN 4B28
Phone: 571/272-2505
Kathleen.Fuller@uspto.gov

Search Notes

sira
Search and Information Resources Administration

ACCESS DB # 178934

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FOR OFFICIAL USE ONLY

Ms Fuller

Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: BEN SACKEY Examiner #: 73489 Date: 2/7/06

Art Unit: 1626 Phone Number: 2-0704 Serial Number: 10/697,545

Location (Bldg/Room#): CM5631 (Mailbox #): 5C18 Results Format Preferred (circle): PAPER DISK

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: Isoxazoline deriv. as inhibitors of Matrix Metalloproteinase

Inventors (please provide full names): C. Xue et al.

SCIENTIFIC REFERENCE
Sci & Tech Inf. Ctr

Earliest Priority Date:

FEB 8 RECD

Pat. & T.M. Office

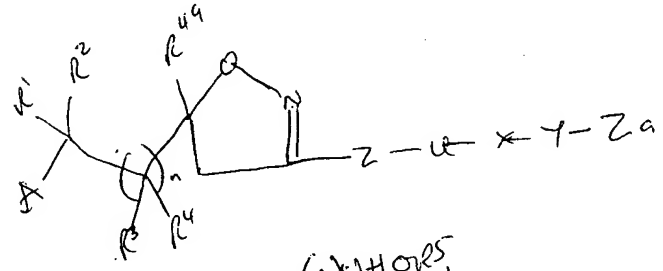
Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

R^1 & R^2 are as defined

R^3 & R^3 are alkylene.



A is -C(O)NHOH, C(O)NHOR5,

U is absent or C_{1-10} alkylene

X is absent or C_{1-10} alkylene

Y is O

Z is C_{3-13} carbocycle substituted with 1-5 R^b

Z^a is 5-14 membered heterocycle containing 1-4 N, O, and S(O)$_{0-2}$ and substituted with 1-5 R^c.

Thanks

STAFF USE ONLY

Searcher: K. Fuller

Searcher Phone #:

Searcher Location:

Date Searcher Picked Up:

Date Completed: 2/10/06

Searcher Prep & Review Time: 30

Online Time: 24

Type of Search

___ NA Sequence (#)

___ AA Sequence (#)

2 Structure (#)

___ Bibliographic

___ Litigation

___ Fulltext

___ Other

Vendors and cost where applicable

✓ STN ___ Dialog

___ Questel/Orbit ___ Lexis/Nexis

___ Westlaw ___ WWW/Internet

___ In-house sequence systems

___ Commercial ___ Oligomer ___ Score/Length

___ Interference ___ SPDI ___ Encode/Transl

___ Other (specify)

=> FILE REG
FILE 'REGISTRY' ENTERED AT 14:40:50 ON 10 FEB 2006

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 8 FEB 2006 HIGHEST RN 873837-20-8
DICTIONARY FILE UPDATES: 8 FEB 2006 HIGHEST RN 873837-20-8

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

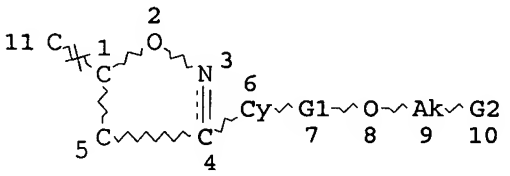
=> FILE HCAPL
FILE 'HCAPLUS' ENTERED AT 14:40:54 ON 10 FEB 2006

FILE COVERS 1907 - 10 Feb 2006 VOL 144 ISS 8
FILE LAST UPDATED: 9 Feb 2006 (20060209/ED)

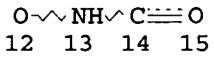
New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> D QUE
L4 STR



54 structures from claim 1 query



REP G1=(0-20) A
VAR G2=H/CY
NODE ATTRIBUTES:
NSPEC IS RC AT 11
CONNECT IS E3 RC AT 14
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L6 54 SEA FILE=REGISTRY SSS FUL L4
L7 6 SEA FILE=HCAPLUS ABB=ON L6

6 CA references

=> D L7 1-6 BIB ABS IND HITSTR

L7 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:430688 HCAPLUS
DN 141:7120
TI Preparation of isoxazoline derivatives as inhibitors of matrix metalloproteinases and/or TNF-α converting enzyme
IN Xue, Chu-Biao; Maduskuie, Thomas P.; Mercer, Stephen E.
PA Bristol-Myers Squibb Company, USA
SO PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

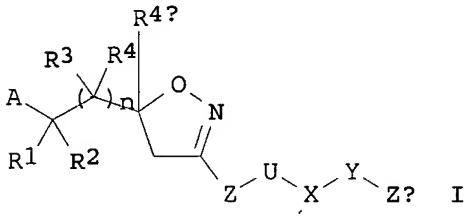
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004043349	A2	20040527	WO 2003-US34391	20031030
	WO 2004043349	A3	20040930		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,

applicants

OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004122005 A1 20040624 US 2003-697545 20031030
PRAI US 2002-424293P P 20021106
OS MARPAT 141:7120
GI



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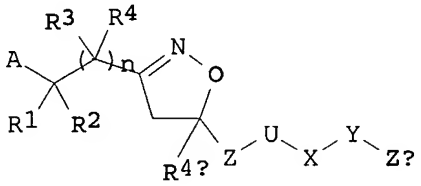

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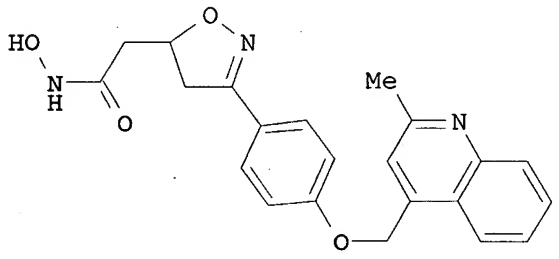

III

AB The title isoxazoline derivs. with general formula of I and II [wherein A = (un)substituted N(OH)COH or CONHOH; U = absent, O, CO, CO2, OCO, (un)substituted NH, CH(OH), CONH, NHCO, etc.; X = absent, alkylene, alkenylene, or alkynylene; Y = absent, O, S, SO, SO2, or CO; Z = substituted carbocycle or heterocycle; Za = H, substituted carbocycle or heterocycle; R1-R4 and R4a = independently Q, alkylene-Q, alkenylene-Q, alkynylene-Q, etc.; Q = H, CHF2, CH2F, CF3, substituted carbocycle, or (hetero)cycle; n = 0 or 1] or pharmaceutically acceptable salts thereof are prepared as inhibitors of matrix metalloproteinases (MMP), TNF-α converting enzyme (TACE), or a combination. For example, the compound III was prepared in a multi-step synthesis. Some of compds. I have inhibitory activity with IC50 of ≤ 0.01 μM against metalloproteinase. I are useful for the treatment of diseases mediated by MMP and/or TACE, such as acute infection, acute phase response, age related macular degeneration, etc. (no data).

IC ICM A61K
CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
ST quinolyl isoxazoline prepn inhibitor matrix metalloproteinase TNF human
IT Disease, animal
(Bechet's; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Inflammation
(Crohn's disease; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Intestine, disease
(Crohn's; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Arthritis
(Felty's syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Infection
(Mycobacterial; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Arthritis
(Reiter's syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Granulomatous disease
(Wegener's granulomatosis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Infection
(acute; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Inflammation
Reproductive system, disease
(adnexitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Liver, disease
(alc.; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Allergy
(allergic asthma; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Asthma
(allergic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Aneurysm
(aortic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Disease, animal
(arthropathy, enteropathic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Disease, animal
(asthenia, postradiation; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Dermatitis
(atopic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Hepatitis
(autoimmune; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Fatigue, biological
(chronic fatigue syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Eye, disease
(cornea, ulcer; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Ulcer
(corneal; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Joint, anatomical
(disease, enteropathic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Heart, disease
(failure; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Muscle, disease

(fibromyalgia, syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Gingiva, disease
Inflammation
(gingivitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Transplant and Transplantation
(graft-vs.-host reaction; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Injury
(hyperoxic alveolar; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Arthritis
(infectious; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Skin
(inflammatory diseases; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Rheumatoid arthritis
(juvenile; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Eye, disease
(macula, senile degeneration; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Disease, animal
(mediated by MMPs and/or TACE; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Glaucoma (disease)
(neovascular; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Lung, disease
(obstructive, chronic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Inflammation
Periodontium, disease
(periodontitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Bone, disease
Inflammation
(polychondritis, relapsing; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Myositis
(polymyositis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT Injury
(post-ischemic reperfusion; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)
IT AIDS (disease)
Acute-phase response
Allergy
Allergy inhibitors
Anaphylaxis
Anorexia
Anti-AIDS agents
Anti-infective agents
Anti-inflammatory agents
Antiarthritics
Antiasthmatics
Antibacterial agents
Antiglaucoma agents

Antipyretics
Antirheumatic agents
Antitumor agents
Asthma
Atherosclerosis
Autoimmune disease
Cachexia
Cardiovascular agents
Cardiovascular system, disease
Coagulants
Coagulation
Dermatomyositis
Emphysema
Fever and Hyperthermia
Fibrosis
Gout
Hemorrhage
Human
Immunomodulators
Inflammation
Lyme disease
Meningitis
Multiple sclerosis
Myasthenia gravis
Osteoarthritis
Psoriasis
Rheumatic fever
Rheumatoid arthritis
Sarcoidosis
Shock (circulatory collapse)
Sjogren's syndrome
(preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Arthritis
(psoriatic arthritis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Connective tissue, disease
(scleroderma; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Sepsis
(sepsis syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Neoplasm
(solid; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Inflammation
Spinal column, disease
(spondylitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Brain, disease
(stroke; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Lupus erythematosus
(systemic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Inflammation
Intestine, disease
(ulcerative colitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Eye, disease
Inflammation
(uveitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or

TACE)

IT Blood vessel, disease
Inflammation
(vasculitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Glucocorticoids
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(withdrawal syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT 17031-92-4, Calcium pyrophosphate dihydrate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(deposition disease; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT **694449-74-6P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT **694449-26-8P 694449-28-0P 694449-30-4P**
694449-32-6P 694449-34-8P 694449-36-0P
694449-38-2P 694449-40-6P 694449-42-8P
694449-44-0P 694449-46-2P 694449-48-4P
694449-50-8P 694449-52-0P 694449-54-2P
694449-56-4P 694449-58-6P 694449-60-0P
694449-62-2P 694449-64-4P 694449-66-6P
694449-68-8P 694449-70-2P 694449-72-4P
694449-76-8P 694449-78-0P 694449-80-4P
694449-82-6P 694449-84-8P 694449-87-1P
694449-89-3P 694449-91-7P 694449-93-9P
694449-95-1P 694449-97-3P 694449-99-5P
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694450-07-2P 694450-09-4P 694450-11-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT 141907-41-7, Matrix metalloproteinase 151769-16-3, TNF-α converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT 53544-45-9P 65832-21-5P 66505-81-5P, 2-(Tetrahydropyran-4-ylidene)ethanol 106928-50-1P 115289-55-9P 116700-73-3P
132079-98-2P 252722-04-6P 441774-63-6P 656803-41-7P 694450-14-1P
694450-16-3P 694450-18-5P 694450-21-0P 694450-23-2P
694450-25-4P 694450-27-6P 694450-31-2P 694450-34-5P
694450-36-7P 694450-38-9P 694450-40-3P 694450-42-5P 694450-44-7P
694450-46-9P 694450-48-1P 694450-50-5P 694450-52-7P 694450-54-9P
694450-56-1P 694450-58-3P 694450-61-8P 694450-63-0P 694450-65-2P
694450-67-4P 694450-71-0P 694450-73-2P 694450-76-5P 694450-79-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

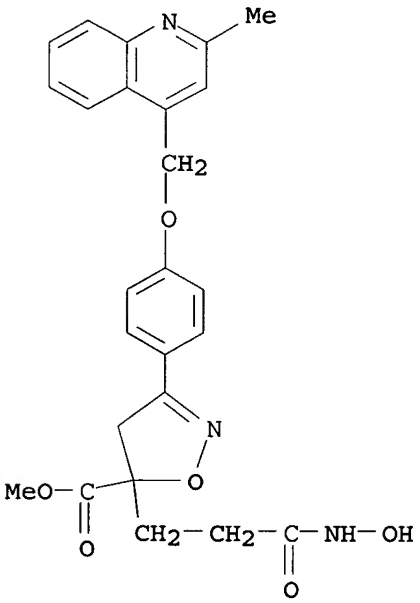
IT 78-39-7, Triethyl orthoacetate 98-01-1, Furan-2-carboxaldehyde, reactions 100-52-7, Benzaldehyde, reactions 109-90-0, Ethyl isocyanate 110-91-8, Morpholine, reactions 123-08-0, p-Hydroxybenzaldehyde 123-75-1, Pyrrolidine, reactions 527-69-5, Furan-2-carbonyl chloride

543-27-1, Isobutyl chloroformate 591-80-0, Pent-4-enoic acid 625-38-7, Vinylacetic acid 1515-75-9, Penta-2,4-dienoic acid methyl ester 3513-81-3, 2-Methylenepropane-1,3-diol 4911-54-0, 4-Methylpent-4-enoic acid ethyl ester 5621-44-3, 2-Methylenepentanedioic acid dimethyl ester 5927-18-4, Trimethyl phosphonoacetate 6044-68-4, 3,3-Dimethoxypropene 6439-57-2 7685-44-1, DL-Allylglycine 10472-24-9, Methyl 2-oxocyclopentanecarboxylate 18162-48-6, tert-Butyldimethylsilyl chloride 24424-99-5, Di-tert-butyl dicarbonate 24731-17-7 36966-11-7 51747-33-2, 2-Methylbut-3-enoic acid methyl ester 57260-71-6 57595-23-0 62327-21-3, tert-Butyl dimethylphosphonoacetate 63721-05-1, 3,3-Dimethylpent-4-enoic acid methyl ester 116616-21-8 138302-49-5 194924-95-3 288399-19-9, 4-Chloromethyl-2-methylquinoline 441773-67-7 694450-87-8 694450-89-0 694450-92-5 694450-95-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT **694449-74-6P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

RN 694449-74-6 HCAPLUS

CN 5-Isoxazolecarboxylic acid, 4,5-dihydro-5-[3-(hydroxyamino)-3-oxopropyl]-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-, methyl ester (9CI) (CA INDEX NAME)



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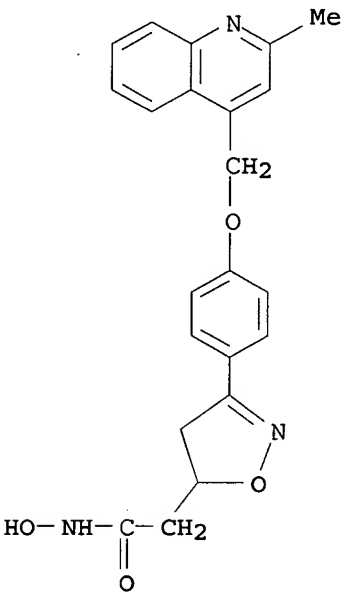
694450-07-2P 694450-09-4P 694450-11-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

RN 694449-26-8 HCAPLUS
CN 5-Isoxazoleacetamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-28-0 HCAPLUS
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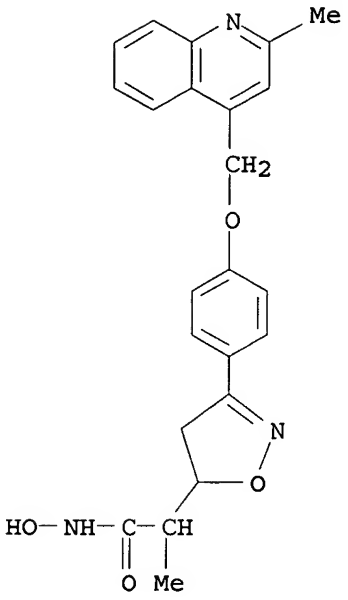
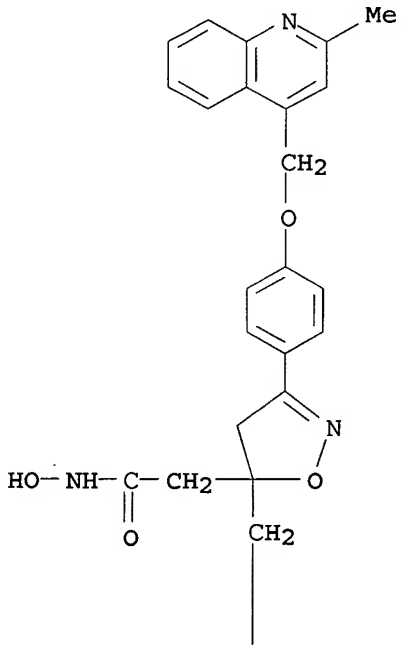


RN 694449-30-4 HCAPLUS
CN 5-Isoxazoleacetamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-(4-morpholinylmethyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



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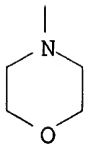

RN 694449-32-6 HCAPLUS
CN 5-Isoxazoleacetamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-(1-piperazinylmethyl)- (9CI) (CA INDEX NAME)

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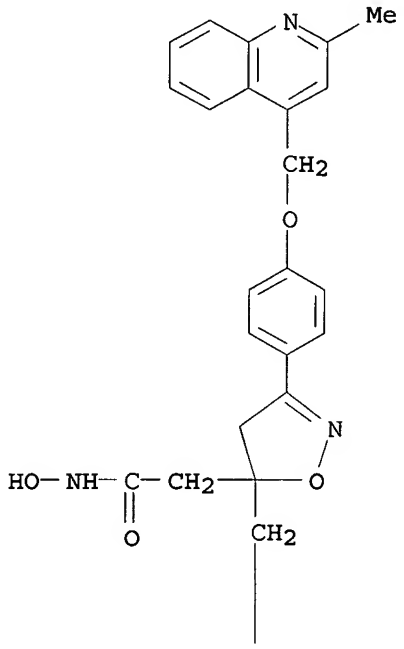

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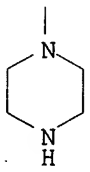
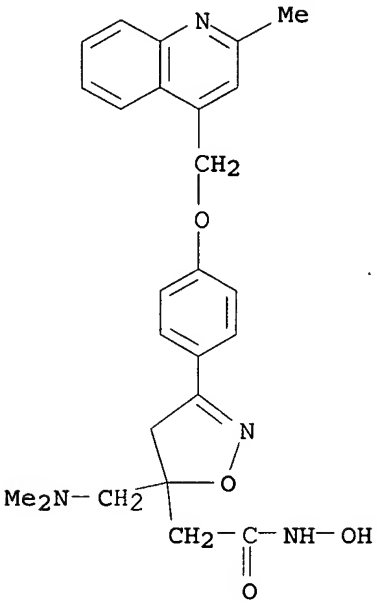
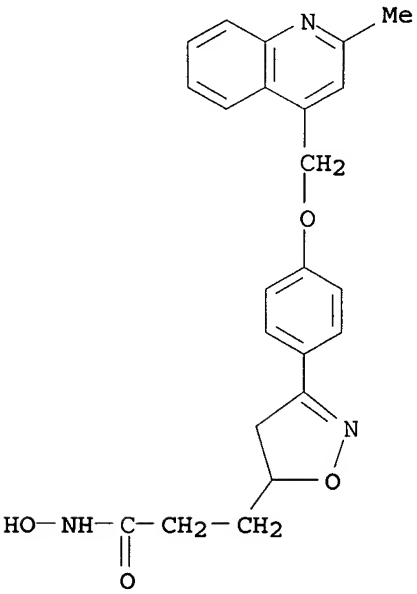


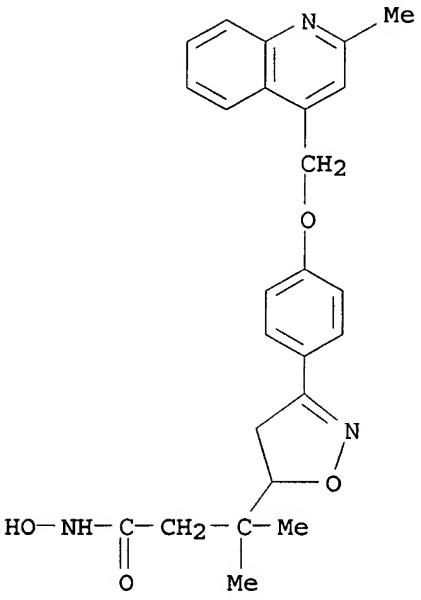
RN 694449-34-8 HCAPLUS
CN 5-Isoxazoleacetamide, 5-[(dimethylamino)methyl]-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-36-0 HCAPLUS
CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-38-2 HCAPLUS
CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-β,β-dimethyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-40-6 HCAPLUS
CN Carbamic acid, [1-[[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]methyl]-2-(hydroxyamino)-2-oxoethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

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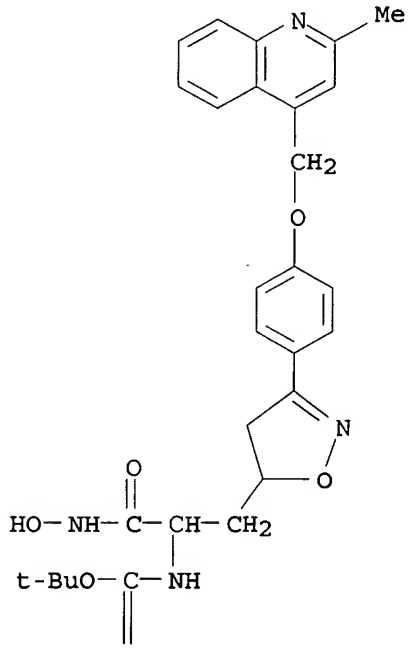

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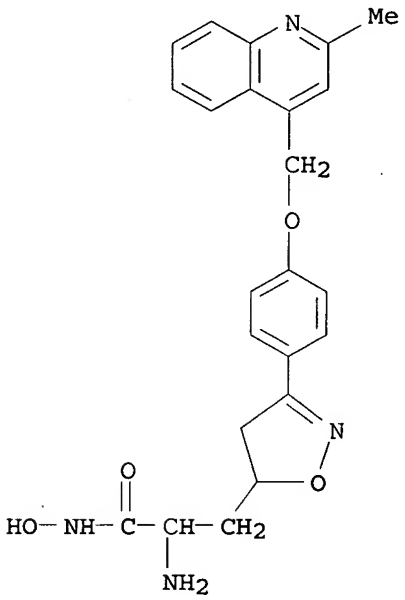
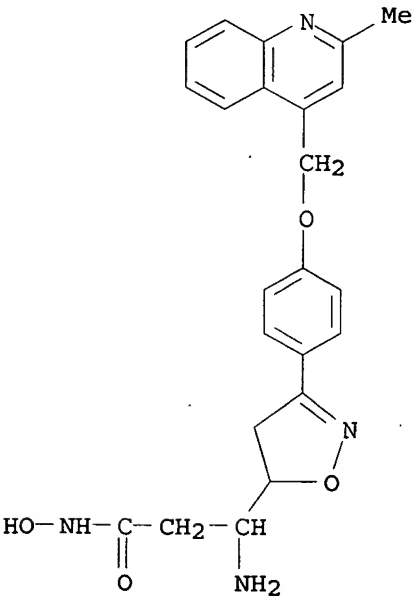
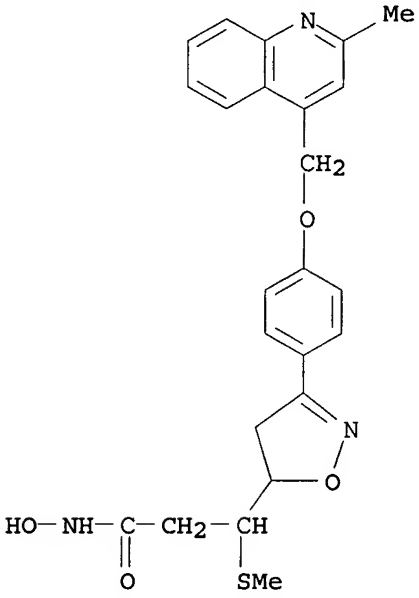
RN 694449-42-8 HCAPLUS
CN 5-Isoxazolepropanamide, α-amino-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-44-0 HCAPLUS
CN 5-Isoxazolepropanamide, β-amino-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-46-2 HCAPLUS
CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-β-(methylthio)- (9CI) (CA INDEX NAME)



RN 694449-48-4 HCAPLUS
CN 4-Morpholinepropanamide, β-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy- (9CI) (CA INDEX NAME)

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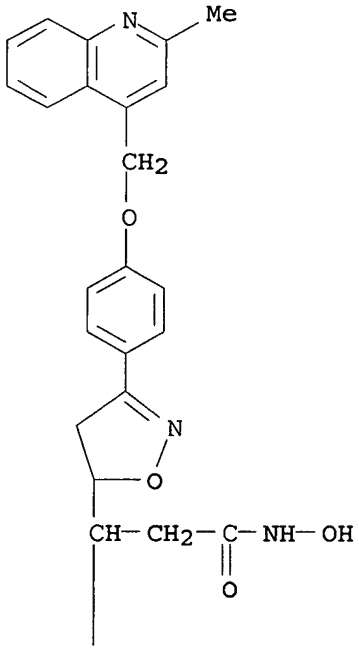

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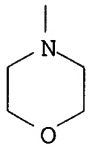
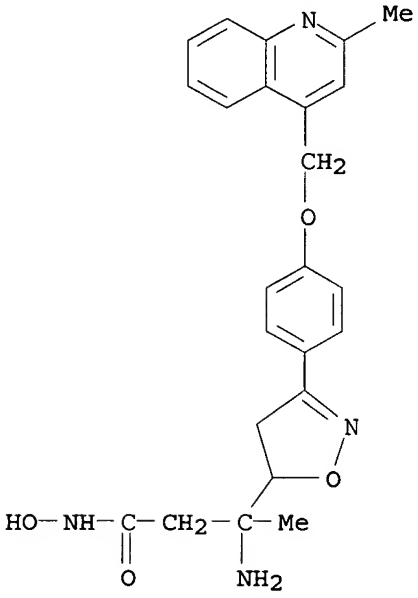


RN 694449-50-8 HCAPLUS
CN 5-Isoxazolepropanamide, β-amino-4,5-dihydro-N-hydroxy-β-methyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-52-0 HCAPLUS
CN 5-Isoxazolepropanamide, β-[(2-furanylcarbonyl)amino]-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)

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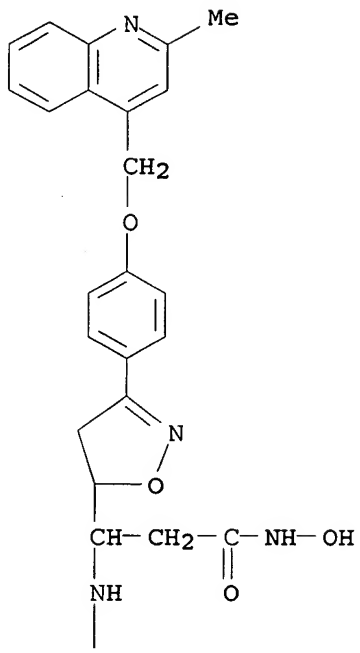

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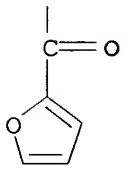

RN 694449-54-2 HCAPLUS
CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-β-1-pyrrolidinyl- (9CI) (CA INDEX NAME)

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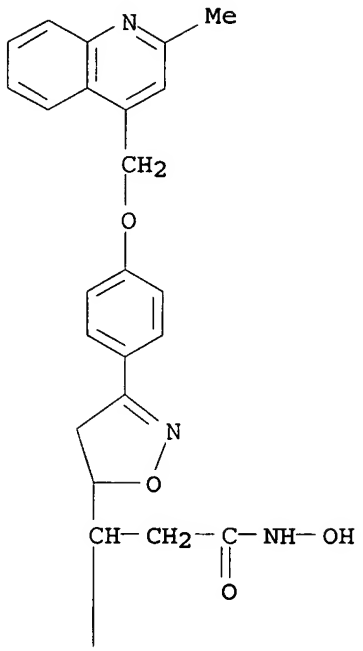

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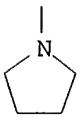
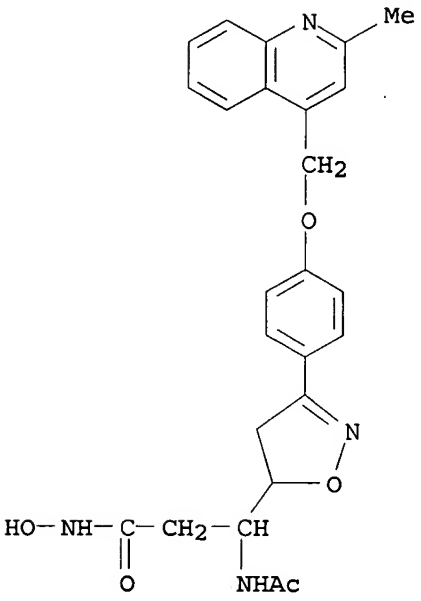
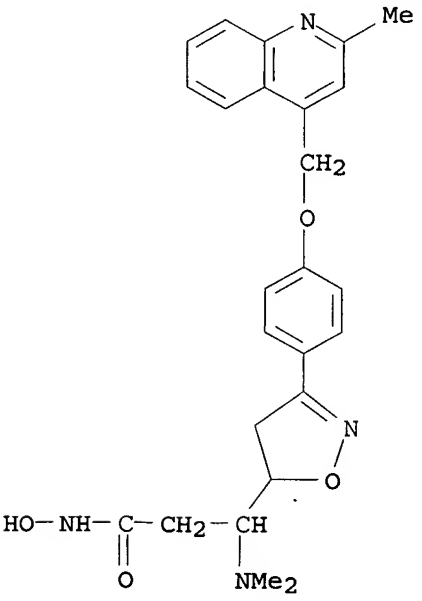


RN 694449-56-4 HCAPLUS
CN 5-Isoxazolepropanamide, β-(acetylamino)-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-58-6 HCAPLUS
CN 5-Isoxazolepropanamide, β-(dimethylamino)-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-60-0 HCAPLUS
CN 5-Isoxazolepropanamide, β-[[(ethylamino)carbonyl]amino]-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)

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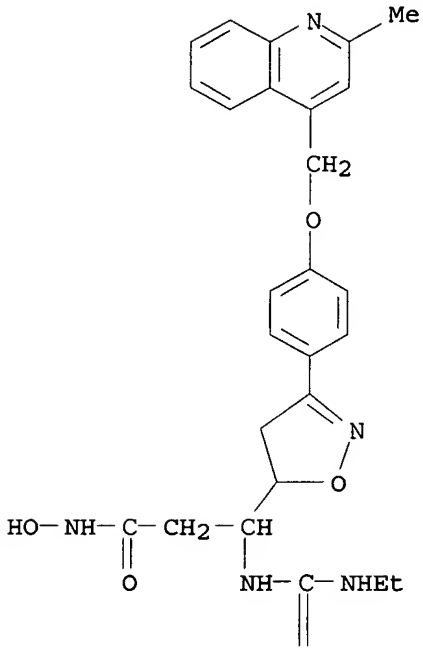

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RN 694449-62-2 HCAPLUS
CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-β-[(methylsulfonyl)amino]- (9CI) (CA INDEX NAME)

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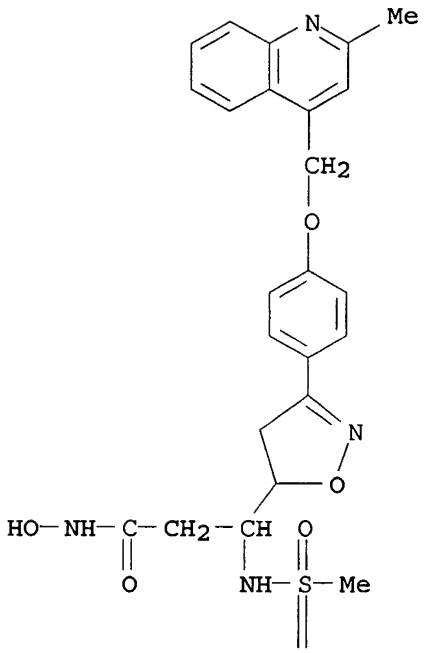

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RN 694449-64-4 HCAPLUS
CN 5-Isoxazolepropanamide, β-[(2-furanylmethyl)amino]-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)

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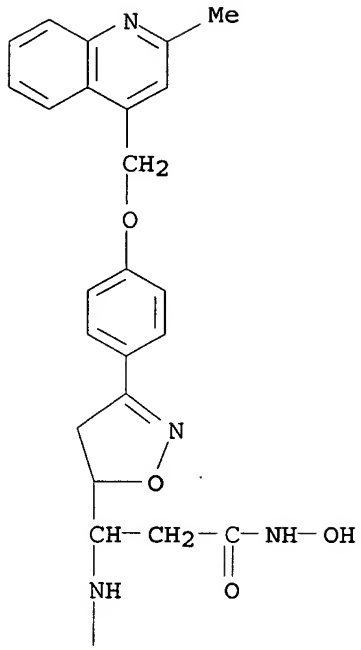

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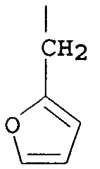
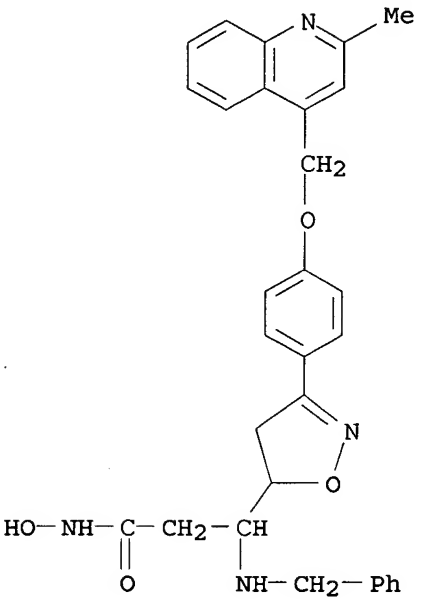


RN 694449-66-6 HCAPLUS
CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-β-[(phenylmethyl)amino]- (9CI) (CA INDEX NAME)



RN 694449-68-8 HCAPLUS
CN Carbamic acid, [1-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-3-(hydroxyamino)-3-oxopropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

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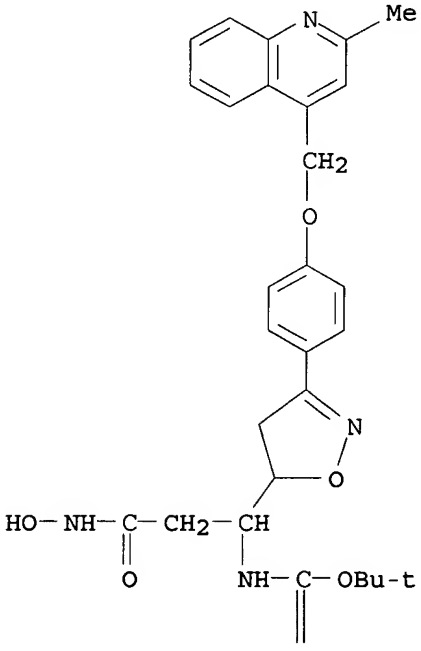

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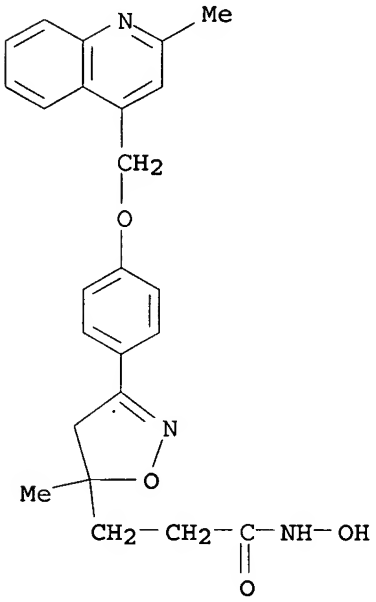
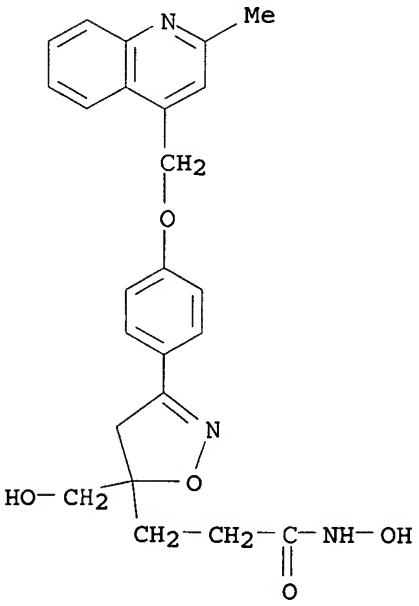
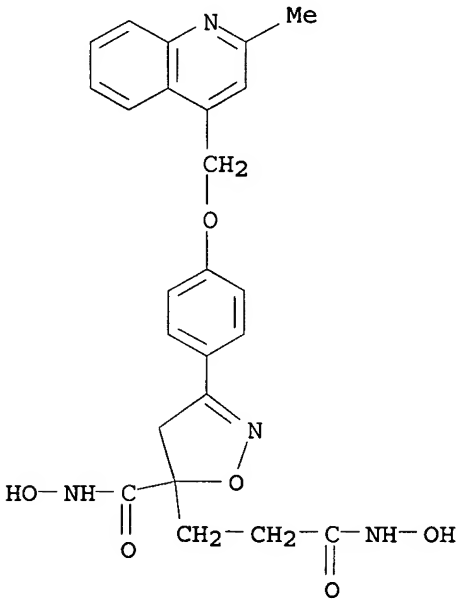
RN 694449-70-2 HCAPLUS
CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-5-methyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



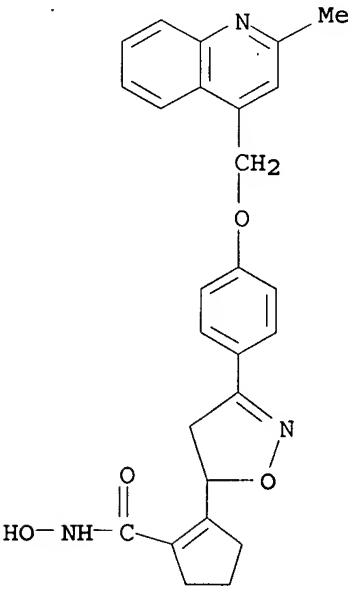
RN 694449-72-4 HCAPLUS
CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-5-(hydroxymethyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



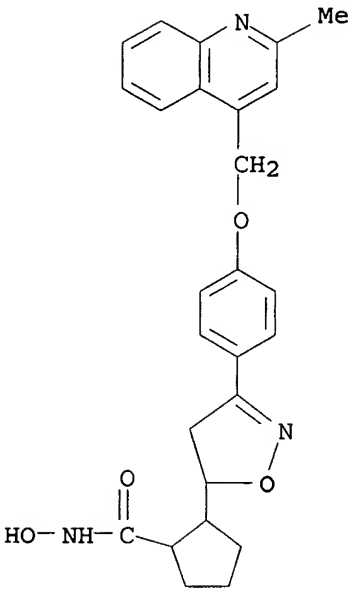
RN 694449-76-8 HCAPLUS
CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-5-[(hydroxyamino)carbonyl]-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



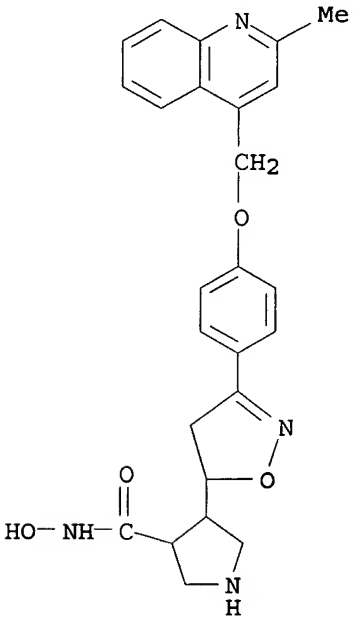
RN 694449-78-0 HCAPLUS
CN 1-Cyclopentene-1-carboxamide, 2-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy- (9CI) (CA INDEX NAME)



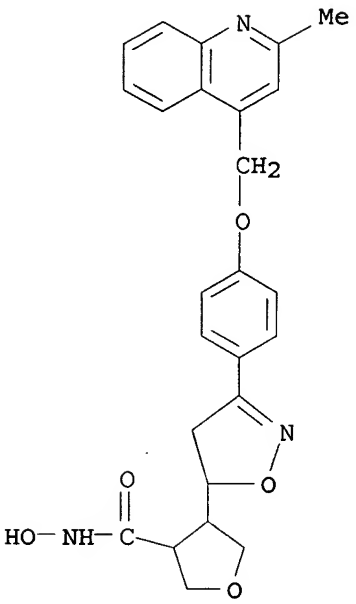
RN 694449-80-4 HCAPLUS
CN Cyclopentanecarboxamide, 2-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy- (9CI) (CA INDEX NAME)



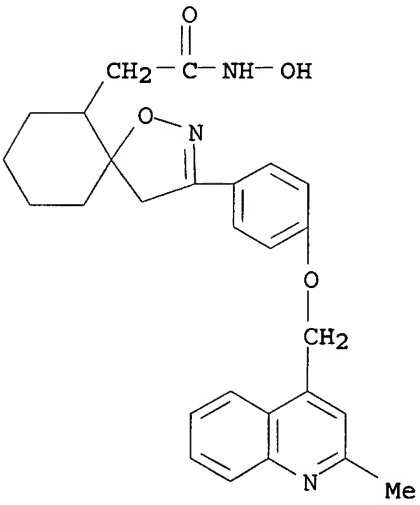
RN 694449-82-6 HCAPLUS
CN 3-Pyrrolidinecarboxamide, 4-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy- (9CI) (CA INDEX NAME)



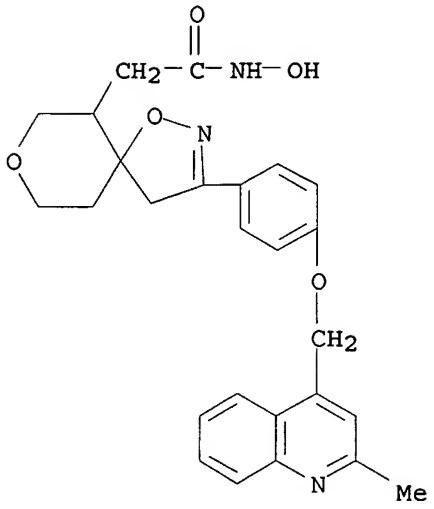
RN 694449-84-8 HCAPLUS
CN 3-Furancarboxamide, 4-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]tetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)



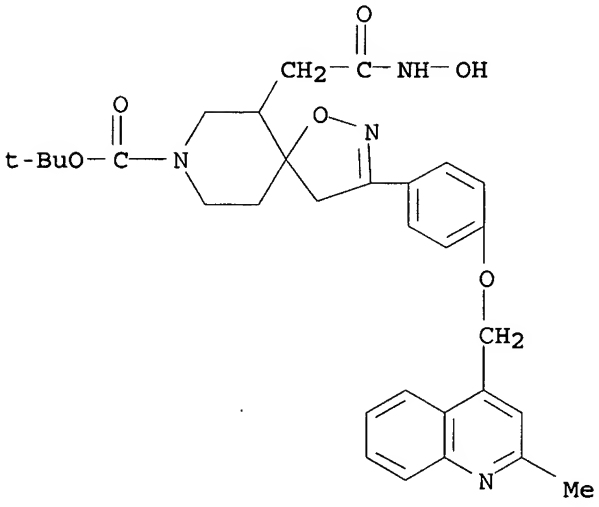
RN 694449-87-1 HCAPLUS
CN 1-Oxa-2-azaspiro[4.5]dec-2-ene-6-acetamide, N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



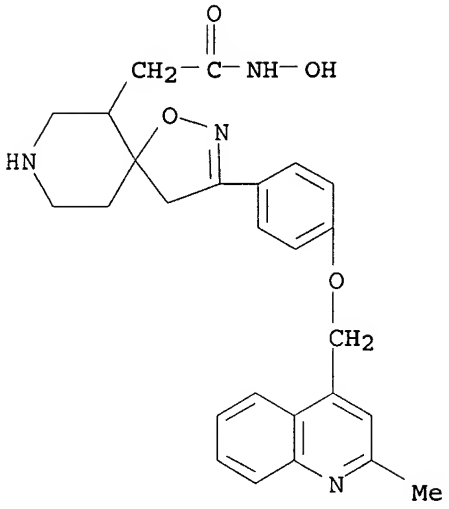
RN 694449-89-3 HCAPLUS
CN 1,8-Dioxa-2-azaspiro[4.5]dec-2-ene-6-acetamide, N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



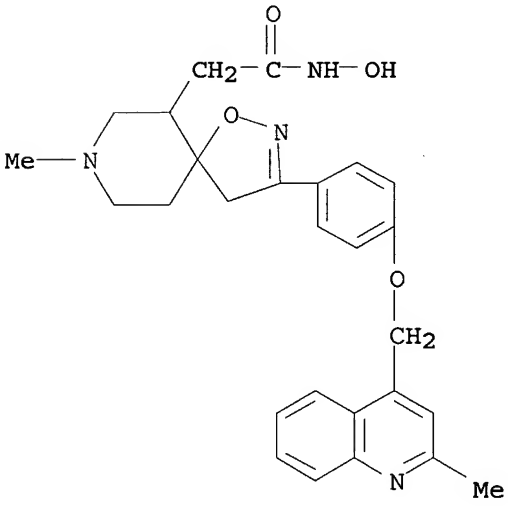
RN 694449-91-7 HCAPLUS
CN 1-Oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylic acid, 6-[2-(hydroxyamino)-2-oxoethyl]-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



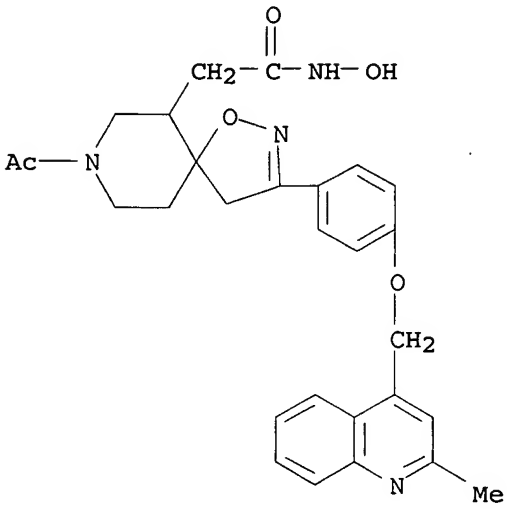
RN 694449-93-9 HCAPLUS
CN 1-Oxa-2,8-diazaspiro[4.5]dec-2-ene-6-acetamide, N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



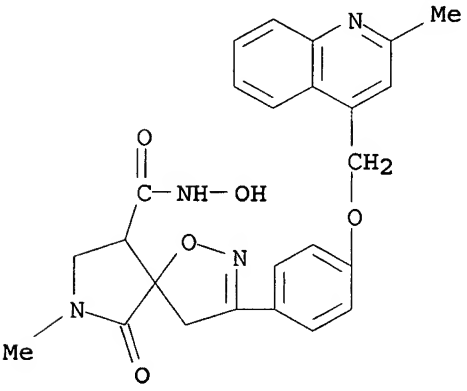
RN 694449-95-1 HCAPLUS
CN 1-Oxa-2,8-diazaspiro[4.5]dec-2-ene-6-acetamide, N-hydroxy-8-methyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



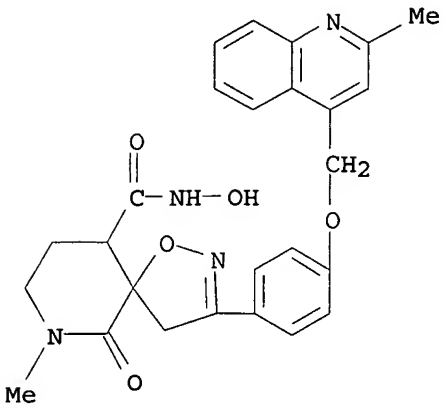
RN 694449-97-3 HCAPLUS
CN 1-Oxa-2,8-diazaspiro[4.5]dec-2-ene-6-acetamide, 8-acetyl-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



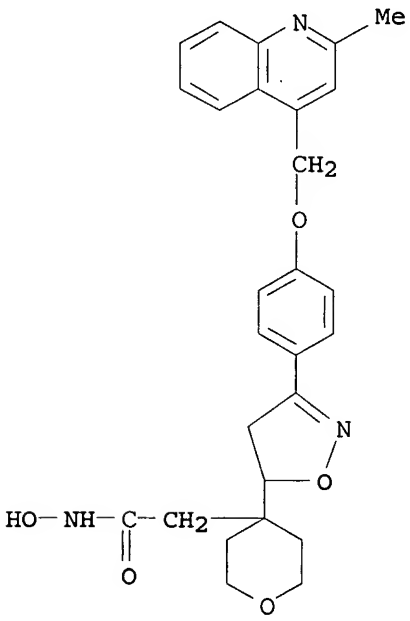
RN 694449-99-5 HCAPLUS
CN 1-Oxa-2,7-diazaspiro[4.4]non-2-ene-9-carboxamide, N-hydroxy-7-methyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-6-oxo- (9CI) (CA INDEX NAME)



RN 694450-01-6 HCAPLUS
CN 1-Oxa-2,7-diazaspiro[4.5]dec-2-ene-10-carboxamide, N-hydroxy-7-methyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-6-oxo- (9CI) (CA INDEX NAME)

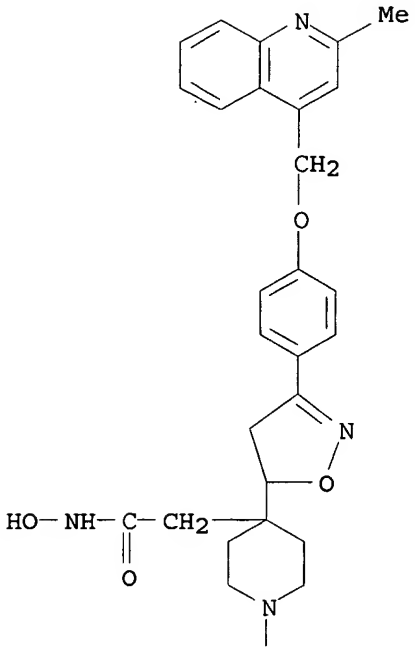


RN 694450-03-8 HCAPLUS
CN 2H-Pyran-4-acetamide, 4-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]tetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)



RN 694450-05-0 HCAPLUS
CN 4-Piperidineacetamide, 1-acetyl-4-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy- (9CI) (CA INDEX NAME)

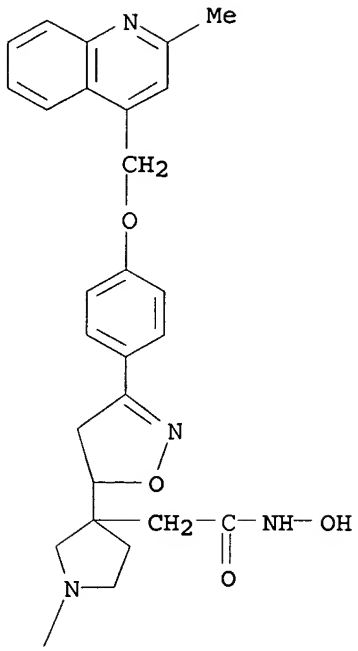
PAGE 1-A



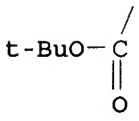
PAGE 2-A

RN 694450-07-2 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-3-[2-(hydroxyamino)-2-oxoethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

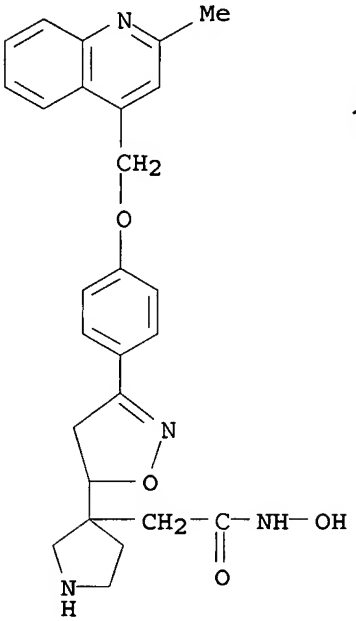
PAGE 1-A



PAGE 2-A



RN 694450-09-4 HCAPLUS
CN 3-Pyrrolidineacetamide, 3-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy- (9CI) (CA INDEX NAME)



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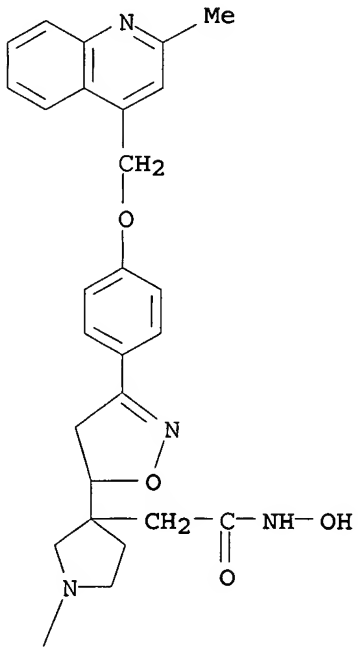
RN 694450-11-8 HCAPLUS
CN 3-Pyrrolidineacetamide, 3-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy-1-methyl- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

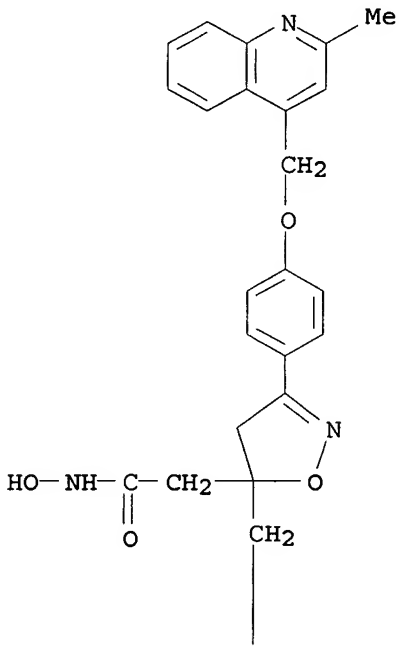
Me

IT **694450-25-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

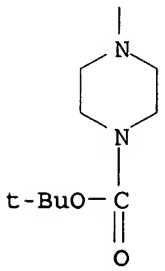
RN 694450-25-4 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-[[4,5-dihydro-5-[2-(hydroxyamino)-2-oxoethyl]-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



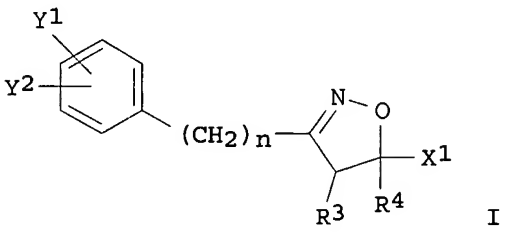
PAGE 2-A



L7 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:623742 HCAPLUS
DN 133:222722
TI Preparation of isoxazoline compounds as inhibitors of TNF release
IN Cohan, Victoria Lee; Kleinman, Edward Fox
PA Pfizer Inc., USA
SO U.S., 19 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6114367	A	20000905	US 1998-187833	19981106
PRAI US 1998-187833		19981106		

OS MARPAT 133:222722
GI



I

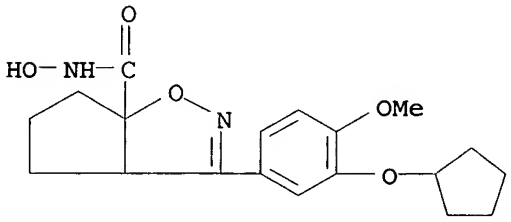
AB Isoxazolines I [X1 = (CH2)qOH, CHR5OH, (CH2)mCONR6OH; n 0-3; Y1, Y2 = H, alkyl, phenylalkyl, CHF2, etc.; R3 = alkyl, phenylalkyl, CF3, etc.; R4 = H, alkyl, Ph, etc.], inhibitors of tumor necrosis factor (no data), were prepared E.g., 3-(3-cyclopentyloxy-4-methoxy)phenyl-2-isoxazoline-5-hydroxamic acid was prepared
IC ICM A61K031-42
ICS A61K031-47
INCL 514378000
CC 28-6 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
ST isoxazoline prepn TNF release inhibitor
IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of isoxazolines as inhibitors of TNF release)
IT **167098-70-6P** 167098-73-9P 167098-74-0P **167098-75-1P**
167098-76-2P 167098-77-3P 167098-78-4P 167098-79-5P
167098-80-8P 167098-81-9P 167098-82-0P 167098-83-1P 167098-84-2P
167098-85-3P 167098-86-4P 167098-87-5P
167098-88-6P 167098-89-7P **167098-92-2P 167098-93-3P**
167099-58-3P 167099-60-7P **172678-99-8P** 290370-53-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of isoxazolines as inhibitors of TNF release)
IT 96-33-3, Methyl acrylate 96-41-3, Cyclopentanol 97-63-2, Ethyl methacrylate 100-39-0, Benzyl bromide 100-83-4, 3-Hydroxybenzaldehyde 121-33-5, Vanillin 123-08-0, 4-Hydroxybenzaldehyde 140-88-5, Ethyl acrylate 621-59-0, Isovanillin 623-70-1, Ethyl trans-crotonate

627-27-0, 3-Buten-1-ol 814-68-6, Acryloyl chloride 2323-74-2
2327-69-7 2627-86-3, (S)-α-Methylbenzylamine 4377-41-7,
2-Chloromethylquinoline 10521-91-2, 5-Phenyl-1-pentanol 17145-91-4,
Triethyl 2-phosphonobutyrate 25662-28-6 31641-78-8 94594-90-8
108448-77-7 290370-54-6 290370-55-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of isoxazolines as inhibitors of TNF release)

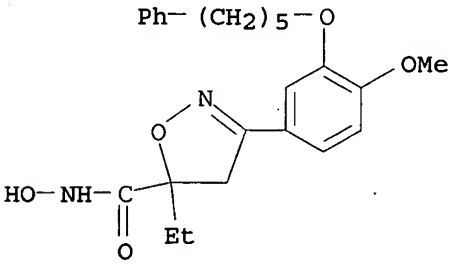
IT 699-06-9P 3070-65-3P 3550-06-9P 3618-37-9P 22286-82-4P
50899-14-4P 51673-94-0P 94594-91-9P 119944-89-7P 158429-65-3P
162279-48-3P 167098-71-7P 167098-94-4P 167098-95-5P 167098-96-6P
167098-97-7P 167098-98-8P 167098-99-9P 167099-00-5P 167099-01-6P
167099-02-7P 167099-03-8P 167099-04-9P 167099-05-0P 167099-06-1P
167099-07-2P 167099-08-3P 167099-09-4P 167099-10-7P 167099-11-8P
167099-12-9P 167099-13-0P 167099-15-2P 167099-16-3P 167099-17-4P
167099-18-5P 167099-20-9P 167099-21-0P 172679-04-8P 172679-07-1P
203062-84-4P 203062-86-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of isoxazolines as inhibitors of TNF release)

IT **167098-70-6P 167098-75-1P 167098-76-2P**
167098-85-3P 167098-86-4P 167098-87-5P
167098-92-2P 167098-93-3P 172678-99-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of isoxazolines as inhibitors of TNF release)

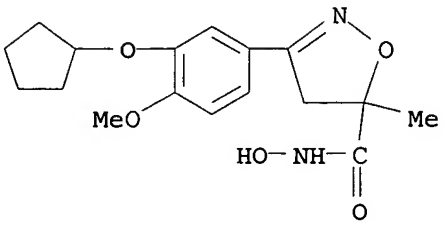
RN 167098-70-6 HCAPLUS
CN 6aH-Cyclopent[d]isoxazole-6a-carboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-3a,4,5,6-tetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)



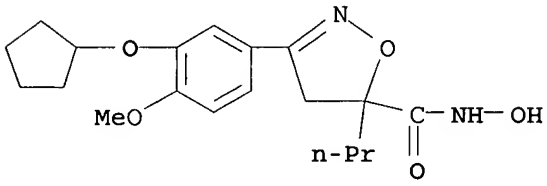
RN 167098-75-1 HCAPLUS
CN 5-Isoxazolecarboxamide, 5-ethyl-4,5-dihydro-N-hydroxy-3-[4-methoxy-3-[(5-phenylpentyl)oxy]phenyl]- (9CI) (CA INDEX NAME)



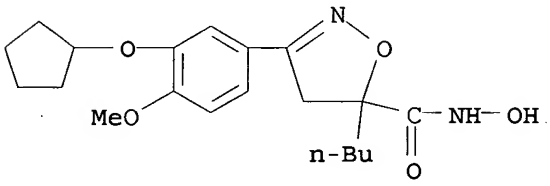
RN 167098-76-2 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)



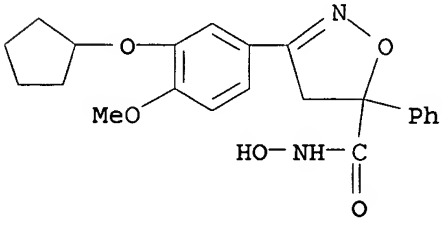
RN 167098-85-3 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-propyl- (9CI) (CA INDEX NAME)



RN 167098-86-4 HCAPLUS
CN 5-Isoxazolecarboxamide, 5-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)

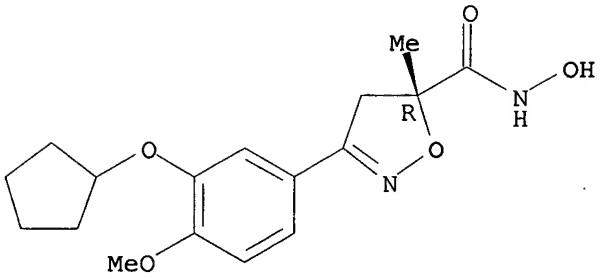


RN 167098-87-5 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-phenyl- (9CI) (CA INDEX NAME)



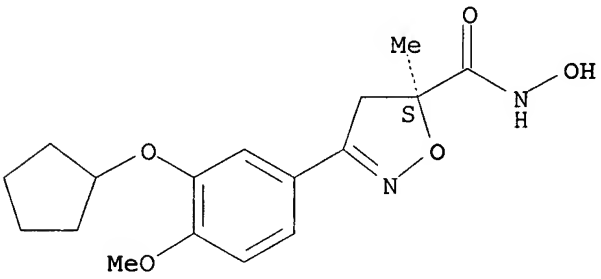
RN 167098-92-2 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

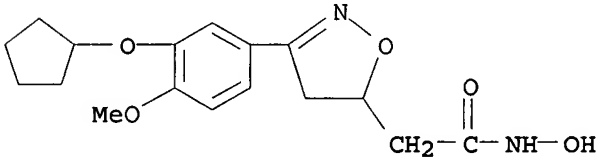


RN 167098-93-3 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172678-99-8 HCAPLUS
CN 5-Isoxazoleacetamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)

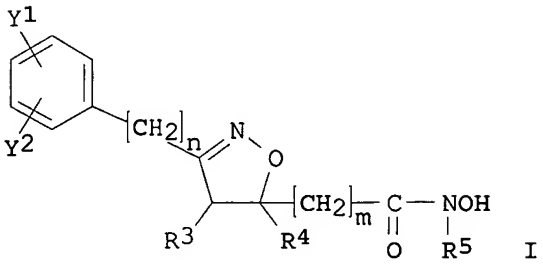


RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:118606 HCAPLUS
DN 128:180405
TI Preparation of isoxazolines as antiinflammatory agents
IN Kleinman, Edward Fox
PA Pfizer Inc., USA
SO U.S., 15 pp., Cont.-in-part of U.S. Ser. No. 262,086,abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI US 5716967 A 19980210 US 1996-640944 19960515
WO 9514681 A1 19950601 WO 1994-IB333 19941026
W: AU, BR, CA, CN, CZ, HU, JP, KR, NO, NZ, PL, RU, US, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
ZA 9409379 A 19960527 ZA 1994-9379 19941125
PRAI US 1993-157248 B2 19931126
US 1994-262086 B2 19940617
WO 1994-IB333 W 19941026
OS MARPAT 128:180405
GI



I

AB The title compds. [I; m, n = 0-3; Y1, Y2 = H, C1-6 alkyl, (un)substituted phenylalkyl, etc.; R3 = H, C1-3 alkyl, fluoro(C1-3)alkyl, etc.; R4 = H, C1-5 alkyl, fluoro(C1-5)alkyl, etc.; R3R4 together with the carbon atoms to which they are attached = carbocyclic ring having 4-7 carbon atoms; R5 = H, C1-3 alkyl], which are selective inhibitors of phosphodiesterase type IV (PDE IV) and therefore useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis, shock, atopic dermatitis, rheumatoid arthritis and osteoarthritis, were prepared Thus, treatment of Et 3-(4-methoxy-3-cyclopentyloxy)-2-isoxazoline-5-carboxylate with H2NOH.HCl in the presence of NaOMe in MeOH afforded I [Y1 = 4-MeO; Y2 = 3-cyclopentyloxy; R3-R5 = H; n = m = 0]. Compds. I are effective in treatment of inflammatory conditions at 0.1-500 mg/day for an average adult patient (70 kg).

IC ICM C07D261-04
ICS A61K031-42
INCL 514313000
CC 28-6 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
ST isoxazoline prepn antiinflammatory phosphodiesterase selective inhibitor
IT Anti-inflammatory agents
(preparation of isoxazolines as antiinflammatory agents)
IT **167098-70-6P** 167098-73-9P 167098-74-0P **167098-75-1P**
167098-76-2P 167098-77-3P 167098-78-4P 167098-79-5P
167098-80-8P 167098-81-9P 167098-82-0P 167098-83-1P 167098-84-2P
167098-85-3P 167098-86-4P 167098-87-5P
167098-88-6P 167098-89-7P **167098-92-2P 167098-93-3P**
172678-99-8P 172679-00-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of isoxazolines as antiinflammatory agents)
IT 96-33-3, Methyl acrylate 96-41-3, Cyclopentanol 97-63-2, Ethyl methacrylate 100-39-0, Benzyl bromide 100-83-4 121-33-5, Vanillin 123-08-0, p-Hydroxybenzaldehyde 140-88-5, Ethyl acrylate 621-59-0, Isovanillin 627-27-0, But-1-en-4-ol 814-68-6, Acryloyl chloride

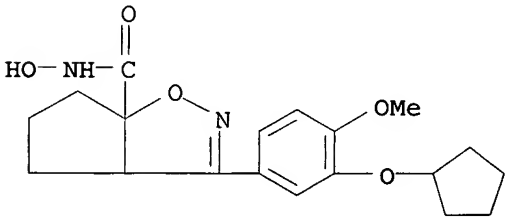
932-90-1, Benzaldehyde oxime 2323-74-2, Triethyl phosphonopentanoate 2627-86-3, (S)-(-)-α-Methylbenzylamine 4134-14-9 4377-41-7, 2-(Chloromethyl)quinoline 10521-91-2, 5-Phenyl-1-pentanol 10544-63-5, Ethyl crotonate 17145-91-4, Triethyl 2-phosphonobutyrate 25662-28-6, Methyl 1-cyclopentenoate 31641-78-8, Triethyl phosphonophenylacetate 108448-77-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of isoxazolines as antiinflammatory agents)

IT 699-06-9P 3070-65-3P 3550-06-9P 3618-37-9P 22286-82-4P 50899-14-4P 51673-94-0P 119944-89-7P 158429-65-3P 162279-48-3P 167098-71-7P 167098-94-4P 167098-95-5P 167098-96-6P 167098-97-7P 167098-98-8P 167098-99-9P 167099-00-5P 167099-01-6P 167099-02-7P 167099-03-8P 167099-04-9P 167099-05-0P 167099-06-1P 167099-07-2P 167099-08-3P 167099-09-4P 167099-10-7P 167099-11-8P 167099-12-9P 167099-13-0P 167099-15-2P 167099-16-3P 167099-17-4P 167099-18-5P 167099-19-6P 167099-20-9P 167099-21-0P 172679-04-8P 203062-84-4P 203062-86-6P 203062-88-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of isoxazolines as antiinflammatory agents)

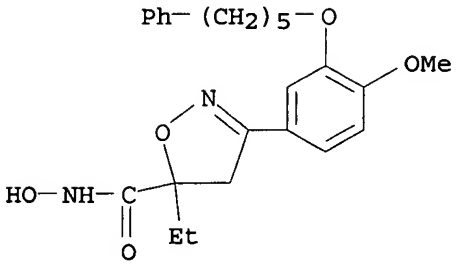
IT 9036-21-9
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(selective inhibitors of PDE IV; preparation of isoxazolines as antiinflammatory agents)

IT **167098-70-6P 167098-75-1P 167098-76-2P 167098-85-3P 167098-86-4P 167098-87-5P 167098-92-2P 167098-93-3P 172678-99-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of isoxazolines as antiinflammatory agents)

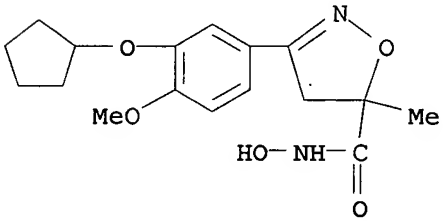
RN 167098-70-6 HCAPLUS
CN 6aH-Cyclopent[d]isoxazole-6a-carboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-3a,4,5,6-tetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)



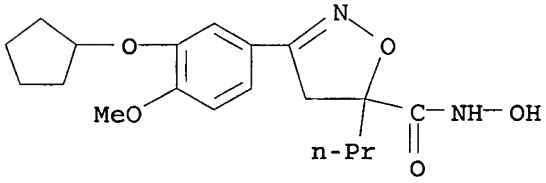
RN 167098-75-1 HCAPLUS
CN 5-Isoxazolecarboxamide, 5-ethyl-4,5-dihydro-N-hydroxy-3-[4-methoxy-3-[(5-phenylpentyl)oxy]phenyl]- (9CI) (CA INDEX NAME)



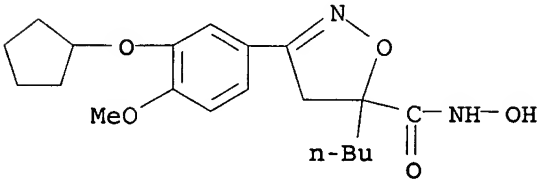
RN 167098-76-2 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)



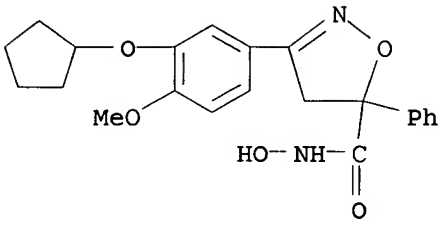
RN 167098-85-3 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-propyl- (9CI) (CA INDEX NAME)



RN 167098-86-4 HCAPLUS
CN 5-Isoxazolecarboxamide, 5-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)

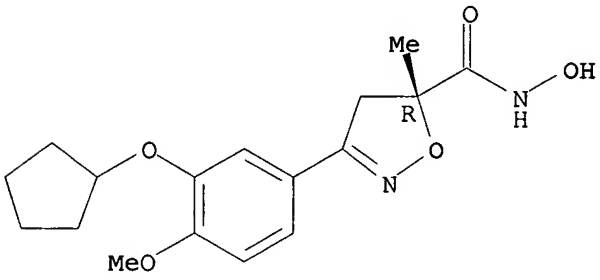


RN 167098-87-5 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-phenyl- (9CI) (CA INDEX NAME)



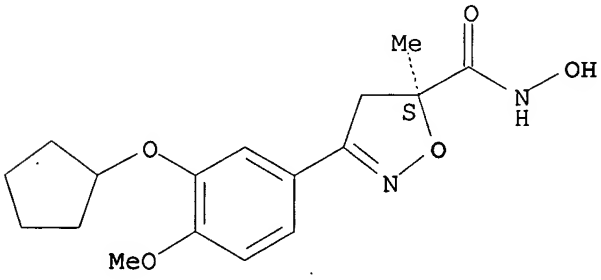
RN 167098-92-2 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

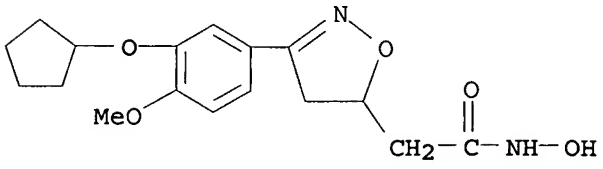


RN 167098-93-3 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172678-99-8 HCAPLUS
CN 5-Isoxazoleacetamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:43032 HCAPLUS
DN 128:188289
TI Striking Effect of Hydroxamic Acid Substitution on the Phosphodiesterase Type 4 (PDE4) and TNFα Inhibitory Activity of Two Series of Rolipram Analogs: Implications for a New Active Site Model of PDE4
AU Kleinman, Edward F.; Campbell, Erin; Giordano, Lisa A.; Cohan, Victoria L.; Jenkinson, Teresa H.; Cheng, John B.; Shirley, John T.; Pettipher, E. Roy; Salter, Eben D.; Hibbs, Tessa A.; DiCapua, Frank M.; Bordner, John
CS Central Research Division, Pfizer Inc, Groton, CT, 06340, USA
SO Journal of Medicinal Chemistry (1998), 41(3), 266-270
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB 3-Aryl-2-isoxazoline-5-hydroxamic acids and their acyclic variant N-aroyl amino hydroxamic acids, patterned after the archetypal phosphodiesterase type 4 (PDE4) inhibitor rolipram, are potent inhibitors of human monocyte (HM) cytosol PDE and LPS-induced release of TNFα in HM and human whole blood (HWB). The SARs of the two series, which run parallel, demonstrates that the hydroxamic acid makes a unique, tight, and highly stereospecific interaction with PDE4. The most potent analog, CP-293121 (I), is 100-fold more potent than rolipram in the HM-PDE4 assay. The therapeutic potential of these compds. in diseases associated with the overprodn. of TNFα is reflected in the IC50 of I in the HWB-TNFα assay, which is 30 nM and to our knowledge is the lowest of any PDE4 inhibitor known. The close structural resemblance of the noncatechol regions of these series to the ribose-3',5'-phosphate group of cAMP as is putatively bound to a divalent metal ion in the active site provides circumstantial evidence that they bind to PDE4, in part, as substrate analogs of cAMP, which has interesting implications for a new active site model of PDE4.
CC 1-3 (Pharmacology)
Section cross-reference(s): 7, 27
ST hydroxamate prepn phosphodiesterase TNF alpha structure; phosphodiesterase 4 inhibitor hydroxamate structure activity; TNF alpha hydroxamate structure activity
IT Enzyme functional sites
(active; preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF-α)
IT Cytoplasm
(cytosol; preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF-α)
IT Blood
Monocyte
(preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF-α)
IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF-α)
IT 167098-73-9P **167098-76-2P** 167098-77-3P **167098-85-3P**
167098-88-6P 167098-89-7P **167098-92-2P** **167098-93-3P**
172678-99-8P 188030-12-8P 188030-18-4P 188030-20-8P
188030-31-1P 188030-32-2P 188030-41-3P 203643-42-9P
203643-46-3P 203643-48-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF-α)

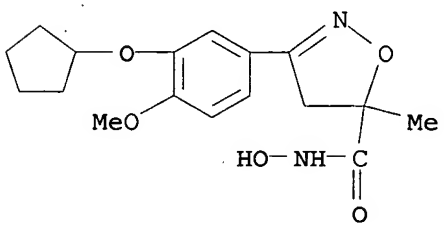
IT 9036-21-9, CAMP phosphodiesterase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF-α)

IT 4519-46-4, Methyl α-bromoacrylate 63648-89-5 79722-09-1 79722-10-4 144036-17-9 162279-48-3 167099-77-6 188029-65-4 203643-49-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF-α)

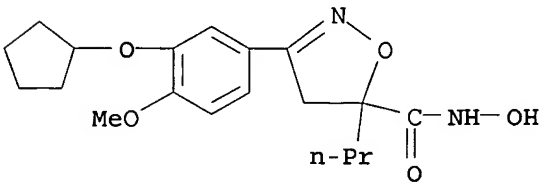
IT 167099-00-5P 167099-01-6P 167099-06-1P 167099-13-0P 167099-15-2P 167099-16-3P 167099-17-4P 167099-18-5P 167099-19-6P 172679-01-5P 188029-39-2P 188029-82-5P 188029-83-6P 188029-97-2P 188029-99-4P 188030-09-3P 203643-40-7P 203643-41-8P 203643-47-4P 203724-92-9P 203724-93-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF-α)

IT **167098-76-2P 167098-85-3P 167098-92-2P 167098-93-3P 172678-99-8P 203643-46-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF-α)

RN 167098-76-2 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)

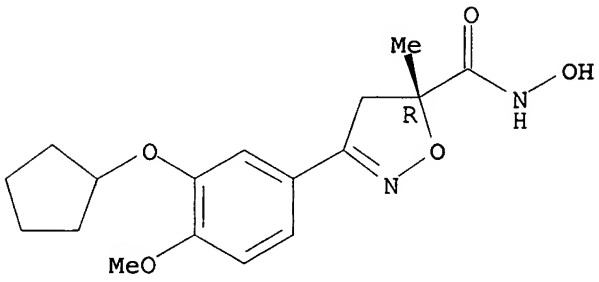


RN 167098-85-3 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-propyl- (9CI) (CA INDEX NAME)



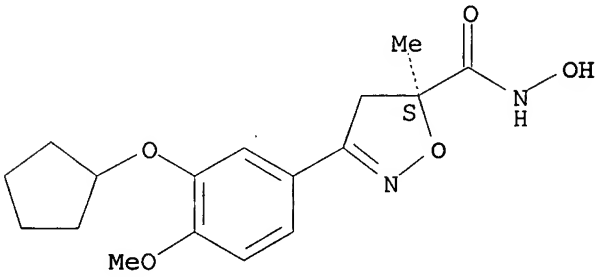
RN 167098-92-2 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

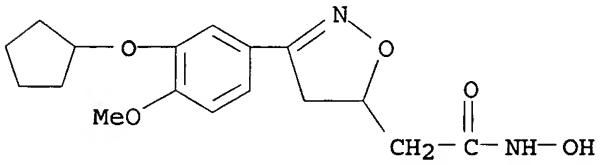


RN 167098-93-3 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5S)- (9CI) (CA INDEX NAME)

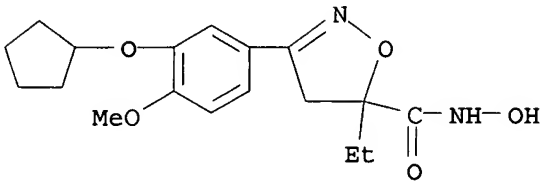
Absolute stereochemistry.



RN 172678-99-8 HCAPLUS
CN 5-Isoxazoleacetamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



RN 203643-46-3 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-5-ethyl-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



L7 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 1995:994847 HCAPLUS
DN 124:117297
TI Isoxazoline compounds as inhibitors of TNF release
IN Cohan, Victoria L.; Kleinman, Edward F.
PA Pfizer Inc., USA
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9524398	A1	19950914	WO 1995-IB78	19950203
	W: AU, CA, CN, FI, JP, KR, MX, NO, NZ, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9514647	A1	19950925	AU 1995-14647	19950203
	AU 684887	B2	19980108		
	EP 749428	A1	19961227	EP 1995-906459	19950203
	EP 749428	B1	19980729		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	CN 1143363	A	19970219	CN 1995-192000	19950203
	JP 09505082	T2	19970520	JP 1995-523329	19950203
	AT 169009	E	19980815	AT 1995-906459	19950203
	ES 2118557	T3	19980916	ES 1995-906459	19950203
	CA 2185019	C	20000808	CA 1995-2185019	19950203
	NZ 278667	A	20001222	NZ 1995-278667	19950203
	IL 112847	A1	19991028	IL 1995-112847	19950302
	ZA 9501909	A	19960909	ZA 1995-1909	19950308
	US 5869511	A	19990209	US 1996-700431	19960905
	FI 9603510	A	19960906	FI 1996-3510	19960906
	NO 9603746	A	19961106	NO 1996-3746	19960906
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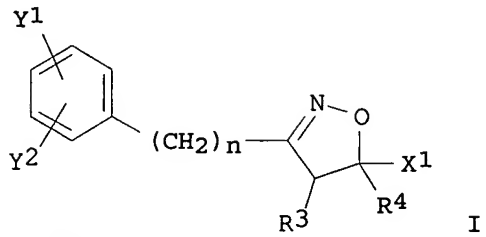
	WO 1995-IB78	W	19950203		

OS MARPAT 124:117297
GI



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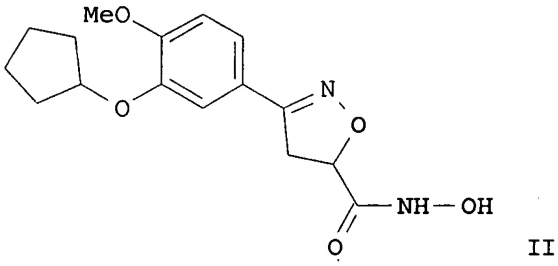


II

AB This invention relates to isoxazoline derivs. I, [X1 = (CH2)qOH, CH(OH)R5, (CH2)mCONR6OH; q, m = 0-5; R5 = C1-4 alkyl; R6 = H, C1-3 alkyl; n = 0-3; Y1, Y2 = H, C1-6 alkyl, (un)substituted phenylalkyl or phenoxyalkyl, cycloalkyl, CHF2, CF3, halo, OR1, OR2; R1 = alkyl, phenylalkyl, CH2F, CHF2, CF3, quinolylalkyl; R2 = alkyl, cycloalkyl, alkoxyalkyl, (un)substituted phenoxyalkyl or phenylalkyl; R3 = H, alkyl, fluoroalkyl, monohydroxyalkyl, alkoxyalkyl, (un)substituted aminoalkyl, cycloalkyl; R4 = H, alkyl, fluoroalkyl, monohydroxyalkyl, Ph, alkoxyalkyl, (un)substituted aminoalkyl; or R3R4 forms C4-7 carbocyclic ring] and their stereoisomeric mixts. or isomers and/or salts, which are inhibitors of tumor necrosis factor (TNF) (no data). I are useful in the treatment or alleviation of inflammatory conditions or diseases, including rheumatoid arthritis, osteoarthritis, asthma, bronchitis, chronic obstructive airway disease, psoriasis, allergic rhinitis, dermatitis, inflammatory bowel disease, sepsis, septic shock, tuberculosis, graft vs. host disease, and cachexia associated with AIDS or cancer. For example, Mitsunobu etherification of isovanillin with cyclopentanol and oximation of the aldehyde function gave 3-cyclopentyloxy-4-methoxybenzaldehyde oxime, which underwent chlorination/dehydrochlorination/1,3-dipolar addition with Et acrylate to form an isoxazoline ring, and finally hydroxamidation with NH2OH.HCl and NaOMe, to give title compound II. Prepns. of 24 I and approx. 40 intermediates are given.

IC ICM C07D261-04
ICS A61K031-42; C07D413-12

CC 28-6 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST isoxazoline prepn inhibitor TNF

IT Allergy inhibitors
Inflammation inhibitors
Tuberculostatics
(preparation of isoxazolines as TNF release inhibitors)

IT Acquired immune deficiency syndrome
Neoplasm
(treatment of associated cachexia; preparation of isoxazolines as TNF release inhibitors)

IT Cachexia
Dermatitis
Hay fever

Psoriasis
Sepsis and Septicemia
(treatment; preparation of isoxazolines as TNF release inhibitors)

IT Inflammation inhibitors
(antiarthritics, preparation of isoxazolines as TNF release inhibitors)

IT Bronchodilators
(antiasthmatics, preparation of isoxazolines as TNF release inhibitors)

IT Lung, disease
(chronic obstructive, treatment; preparation of isoxazolines as TNF release inhibitors)

IT Bronchi
(diseases, bronchitis, treatment; preparation of isoxazolines as TNF release inhibitors)

IT Transplant and Transplantation
(graft-vs.-host reaction, treatment; preparation of isoxazolines as TNF release inhibitors)

IT Intestine, disease
(inflammatory, treatment; preparation of isoxazolines as TNF release inhibitors)

IT Shock
(septic, treatment; preparation of isoxazolines as TNF release inhibitors)

IT Lymphokines and Cytokines
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(tumor necrosis factor, preparation of isoxazolines as TNF release inhibitors)

IT 699-06-9P, 4-Hydroxybenzaldehyde oxime 3070-65-3P, Ethyl 2-methylenebutyrate 50899-14-4P 51673-94-0P, 3-Hydroxy-4-methoxybenzaldehyde oxime 65818-31-7P 66551-91-5P 94594-91-9P 101074-24-2P 119944-89-7P 158429-65-3P, 4-Methoxy-3-(5-phenylpentyloxy)benzaldehyde 162279-48-3P, 4-Methoxy-3-cyclopentyloxybenzaldehyde oxime 167098-72-8P 167098-94-4P, 4-Methoxy-3-(5-phenylpentyloxy)benzaldehyde oxime 167098-95-5P, 3-Cyclopentyloxybenzaldehyde oxime 167098-96-6P 167098-97-7P 167098-98-8P 167098-99-9P 167099-00-5P 167099-01-6P 167099-02-7P 167099-03-8P 167099-04-9P 167099-05-0P 167099-07-2P 167099-08-3P 167099-09-4P 167099-10-7P 167099-11-8P 167099-12-9P 167099-15-2P 167099-16-3P 167099-17-4P 167099-18-5P 167099-19-6P 167099-20-9P 172679-01-5P 172679-02-6P 172679-03-7P 172679-04-8P 172679-05-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of isoxazolines as TNF release inhibitors)

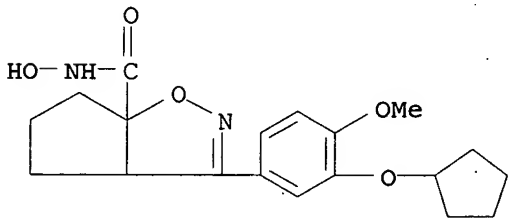
IT **167098-70-6P** 167098-73-9P 167098-74-0P **167098-75-1P** **167098-76-2P** 167098-77-3P 167098-78-4P 167098-79-5P 167098-81-9P 167098-82-0P 167098-83-1P 167098-84-2P **167098-85-3P** **167098-86-4P** **167098-87-5P** 167098-88-6P 167098-89-7P **167098-92-2P** **167098-93-3P** 167099-58-3P 167099-60-7P **172678-99-8P** 172679-00-4P 172779-36-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of isoxazolines as TNF release inhibitors)

IT 50-00-0, Formaldehyde, reactions 74-88-4, Methyl iodide, reactions 96-33-3, Methyl acrylate 96-41-3, Cyclopentanol 97-63-2, Ethyl methacrylate 100-39-0, Benzyl bromide 100-83-4 121-33-5, Vanillin 123-08-0, p-Hydroxybenzaldehyde 140-88-5, Ethyl acrylate 621-59-0, Isovanillin 814-68-6, Acryloyl chloride 932-90-1, Benzaldehyde oxime 4134-14-9, Triethyl 2-phosphonohexanoate 4229-44-1, N-Methylhydroxylamine hydrochloride 4377-41-7, 2-(Chloromethyl)quinoline

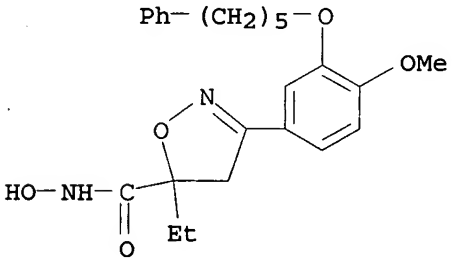
5470-11-1, Hydroxylamine hydrochloride 10521-91-2, 5-Phenyl-1-pentanol 10544-63-5, Ethyl crotonate 17145-91-4, Triethyl 2-phosphonobutyrate 25662-28-6, Methyl 1-cyclopentenoate 31641-78-8, Triethyl phosphonophenylacetate 35051-49-1, Triethyl 2-phosphonopentanoate 39161-19-8, 3-Penten-1-ol 94594-90-8 108448-77-7, (+)-L-2,10-Camphor sultam 172679-06-0 172679-07-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of isoxazolines as TNF release inhibitors)

IT **167098-70-6P 167098-75-1P 167098-76-2P 167098-85-3P 167098-86-4P 167098-87-5P 167098-92-2P 167098-93-3P 172678-99-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of isoxazolines as TNF release inhibitors)

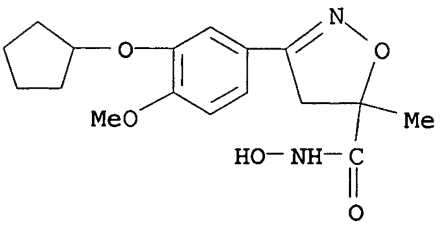
RN 167098-70-6 HCAPLUS
CN 6aH-Cyclopent[d]isoxazole-6a-carboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-3a,4,5,6-tetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)



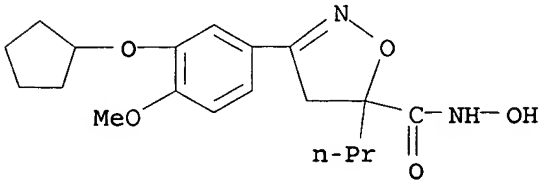
RN 167098-75-1 HCAPLUS
CN 5-Isoxazolecarboxamide, 5-ethyl-4,5-dihydro-N-hydroxy-3-[4-methoxy-3-[(5-phenylpentyl)oxy]phenyl]- (9CI) (CA INDEX NAME)



RN 167098-76-2 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)



RN 167098-85-3 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-propyl- (9CI) (CA INDEX NAME)



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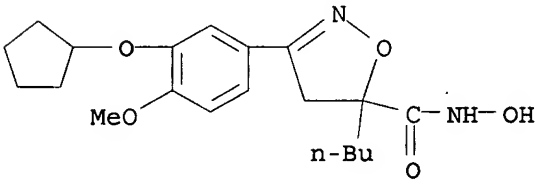

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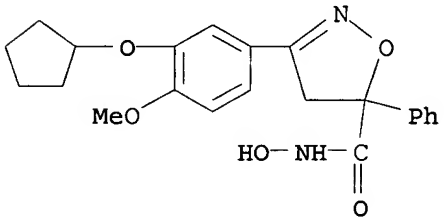
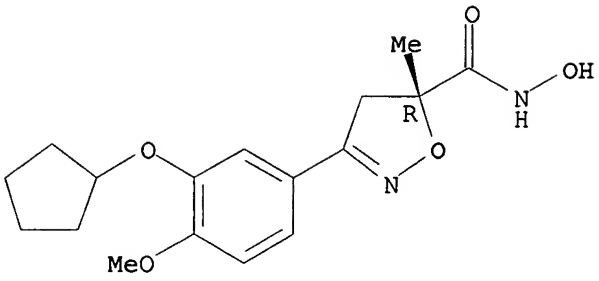
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-phenyl- (9CI) (CA INDEX NAME)



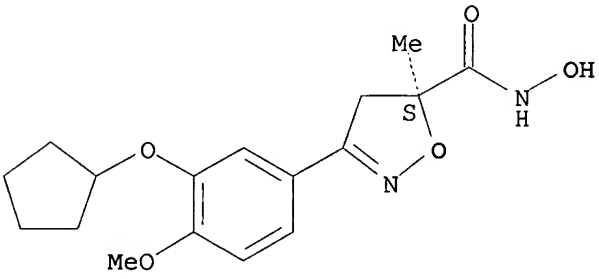
RN 167098-92-2 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 167098-93-3 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172678-99-8 HCAPLUS
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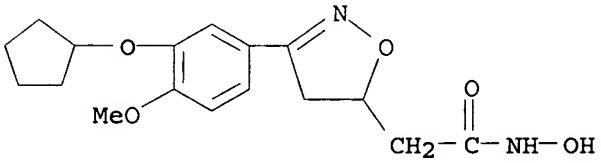


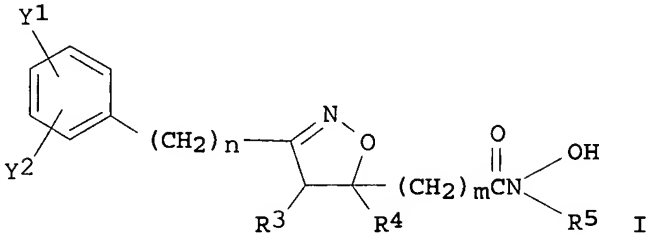
L7 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 1995:763861 HCAPLUS
DN 123:169610
TI Isoxazoline compounds as antiinflammatory agents
IN Kleinman, Edward F.
PA Pfizer Inc., USA
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9514681	A1	19950601	WO 1994-IB333	19941026
	W: AU, BR, CA, CN, CZ, HU, JP, KR, NO, NZ, PL, RU, US, US				

	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2176255	AA	19950601	CA 1994-2176255	19941026
	CA 2176255	C	19990223		
	AU 9478218	A1	19950613	AU 1994-78218	19941026
	AU 687452	B2	19980226		
	EP 730588	A1	19960911	EP 1994-929001	19941026
	EP 730588	B1	19970702		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	CN 1136314	A	19961120	CN 1994-194274	19941026
	CN 1046274	B	19991110		
	JP 09500147	T2	19970107	JP 1994-514933	19941026
	BR 9408174	A	19970527	BR 1994-8174	19941026
	AT 154932	E	19970715	AT 1994-929001	19941026
	ES 2104424	T3	19971001	ES 1994-929001	19941026
	HU 76784	A2	19971128	HU 1996-1412	19941026
	CZ 283564	B6	19980513	CZ 1996-1510	19941026
	IL 111670	A1	19980816	IL 1994-111670	19941117
	FI 9405557	A	19950527	FI 1994-5557	19941125
	ZA 9409379	A	19960527	ZA 1994-9379	19941125
	US 5716967	A	19980210	US 1996-640944	19960515
	NO 9602127	A	19960524	NO 1996-2127	19960524
PRAI	US 1993-157248	A2	19931126		
	US 1994-262086	A2	19940617		
	WO 1994-IB333	W	19941026		

OS CASREACT 123:169610; MARPAT 123:169610

GI



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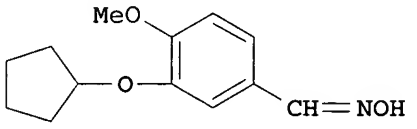

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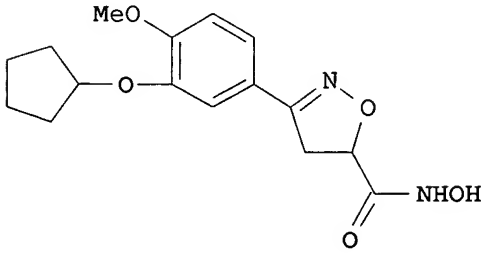


III

AB The invention relates to new isoxazolines I [m, n = 0-3; Y1, Y2 = H, alkyl, (un)substituted phenylalkyl or phenoxyalkyl, cycloalkyl, CHF2, CF3,

halo, OR1, OR2; R1 = alkyl, phenylalkyl, CH2F, CHF2, CF3; R2 = alkyl, cycloalkyl, alkoxyalkyl, (un)substituted phenoxyalkyl, phenylalkyl, or indanylalkyl, bicycloalkyl; R3 = H, alkyl, fluoroalkyl, hydroxyalkyl, alkoxyalkyl; R4 = H, alkyl, fluoroalkyl, hydroxyalkyl, Ph, alkoxyalkyl, (di)(alkyl)aminoalkyl, alkanoylaminoalkyl, cycloalkyl; or R3R4 form carbocyclic ring of 4-7 atoms; R5 = H, alkyl]. I are selective inhibitors of phosphodiesterase type IV (no data), and are useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, etc. For example, etherification of isovanillin with cyclopentanol by the Mitsunobu method, and oximation of the resultant aldehyde-ether, gave oxime II. Reaction of II with N-chlorosuccinimide and pyridine, followed by cyclization of the product with Et acrylate in the presence of Et3N in situ, and reaction of the Et ester product with NH2OH.HCl and NaOMe in MeOH, gave title compound III. Prepns. of approx. 20 I and 40 precursors are described.

IC ICM C07D261-04
ICS A61K031-42

CC 28-6 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST isoxazoline hydroxamic acid prepn antiinflammatory; phosphodiesterase inhibitor isoxazoline hydroxamic acid prepn; PDE IV inhibitor isoxazoline hydroxamic acid

IT Allergy inhibitors
Inflammation inhibitors
(preparation of isoxazolines as PDE type IV inhibitors)

IT Acquired immune deficiency syndrome
Dermatitis
Psoriasis
Shock
(treatment; preparation of isoxazolines as PDE type IV inhibitors)

IT Inflammation inhibitors
(antiarthritics, preparation of isoxazolines as PDE type IV inhibitors)

IT Bronchodilators
(antiasthmatics, preparation of isoxazolines as PDE type IV inhibitors)

IT Lung, disease
(chronic obstructive, treatment; preparation of isoxazolines as PDE type IV inhibitors)

IT Bronchi
(diseases, bronchitis, treatment; preparation of isoxazolines as PDE type IV inhibitors)

IT 699-06-9P, 4-Hydroxybenzaldehyde oxime 3070-65-3P, Ethyl 2-methylenebutyrate 3550-06-9P, Ethyl 2-propylacrylate 3618-37-9P, Ethyl 2-butylacrylate 22286-82-4P, Ethyl 2-phenylacrylate 50899-14-4P, 3-Phenyl-2-isoxazoline-5-carboxylic acid ethyl ester 51673-94-0P, 3-Hydroxy-4-methoxybenzaldehyde oxime 119944-89-7P 158429-65-3P, 4-Methoxy-3-(5-phenylpentyloxy)benzaldehyde 162279-48-3P, 3-(Cyclopentyloxy)-4-methoxybenzaldehyde oxime 167098-71-7P 167098-72-8P 167098-94-4P, 4-Methoxy-3-(5-phenylpentyloxy)benzaldehyde oxime 167098-95-5P, 3-(Cyclopentyloxy)benzaldehyde oxime 167098-96-6P, 4-(Cyclopentyloxy)-3-methoxybenzaldehyde oxime 167098-97-7P 167098-98-8P 167098-99-9P 167099-00-5P 167099-01-6P 167099-02-7P 167099-03-8P 167099-04-9P 167099-05-0P 167099-06-1P 167099-07-2P 167099-08-3P 167099-09-4P, 3-(3,4-Dimethoxyphenyl)-2-isoxazoline-5-carboxylic acid methyl ester 167099-10-7P 167099-11-8P 167099-12-9P 167099-13-0P 167099-15-2P 167099-16-3P 167099-17-4P 167099-18-5P 167099-19-6P 167099-20-9P 167099-21-0P 172679-04-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of isoxazolines as PDE type IV inhibitors)

IT **167098-70-6P** 167098-73-9P 167098-74-0P **167098-75-1P**

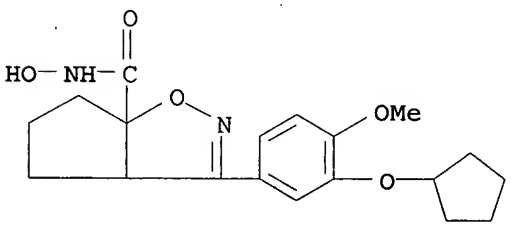
167098-76-2P 167098-77-3P 167098-78-4P 167098-79-5P
167098-80-8P 167098-81-9P 167098-82-0P 167098-83-1P 167098-84-2P,
3-Phenyl-2-isoxazoline-5-hydroxamic acid **167098-85-3P**
167098-86-4P 167098-87-5P 167098-88-6P 167098-89-7P
167098-92-2P 167098-93-3P 172678-99-8P
172679-00-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of isoxazolines as PDE type IV inhibitors)

IT 9025-82-5, Phosphodiesterase
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(preparation of isoxazolines as PDE type IV inhibitors)

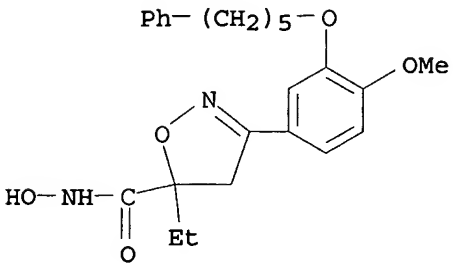
IT 50-00-0, Formaldehyde, reactions 74-88-4, Methyl iodide, reactions 96-33-3, Methyl acrylate 96-41-3, Cyclopentanol 97-63-2, Ethyl methacrylate 100-39-0, Benzyl bromide 100-83-4 121-33-5, Vanillin 123-08-0, p-Hydroxybenzaldehyde 140-88-5, Ethyl acrylate 621-59-0, Isovanillin 627-27-0, 3-Buten-1-ol 814-68-6, Acryloyl chloride 932-90-1, Benzaldehyde oxime 2627-86-3, (S)-(-)-α-Methylbenzylamine 4134-14-9, Triethyl 2-phosphonohexanoate 4229-44-1, N-Methylhydroxylamine hydrochloride 4377-41-7, 2-(Chloromethyl)quinoline 5470-11-1, Hydroxylamine hydrochloride 10521-91-2, 5-Phenyl-1-pentanol 10544-63-5, Ethyl crotonate 17145-91-4, Triethyl 2-phosphonobutyrate 25662-28-6, Methyl 1-cyclopentenoate 31641-78-8, Triethyl phosphonophenylacetate 35051-49-1, Triethyl 2-phosphonopentanoate 94594-91-9 108448-77-7, (+)-L-2,10-Camphorsultam
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of isoxazolines as PDE type IV inhibitors)

IT **167098-70-6P 167098-75-1P 167098-76-2P**
167098-85-3P 167098-86-4P 167098-87-5P
167098-92-2P 167098-93-3P 172678-99-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of isoxazolines as PDE type IV inhibitors)

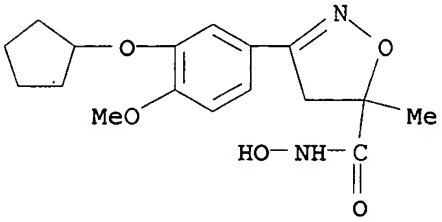
RN 167098-70-6 HCAPLUS
CN 6aH-Cyclopent[d]isoxazole-6a-carboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-3a,4,5,6-tetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)



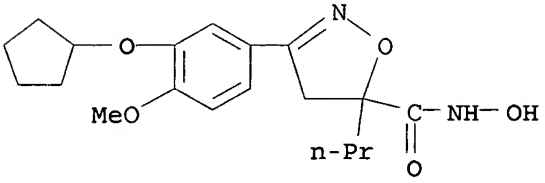
RN 167098-75-1 HCAPLUS
CN 5-Isoxazolecarboxamide, 5-ethyl-4,5-dihydro-N-hydroxy-3-[4-methoxy-3-[(5-phenylpentyl)oxy]phenyl]- (9CI) (CA INDEX NAME)



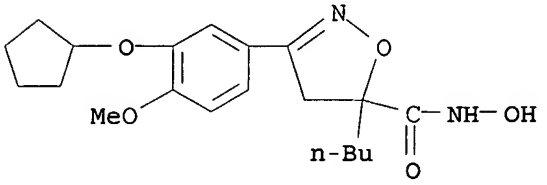
RN 167098-76-2 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)



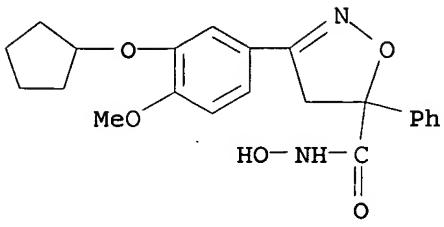
RN 167098-85-3 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-propyl- (9CI) (CA INDEX NAME)



RN 167098-86-4 HCAPLUS
CN 5-Isoxazolecarboxamide, 5-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)

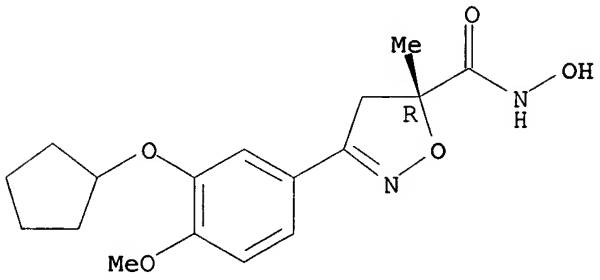


RN 167098-87-5 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-phenyl- (9CI) (CA INDEX NAME)



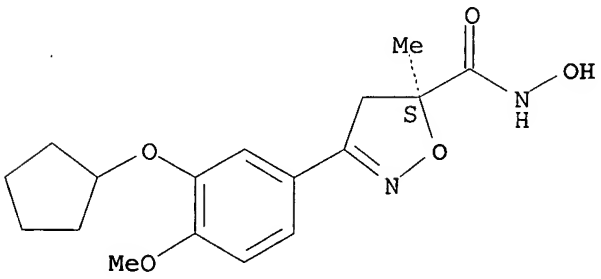
RN 167098-92-2 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

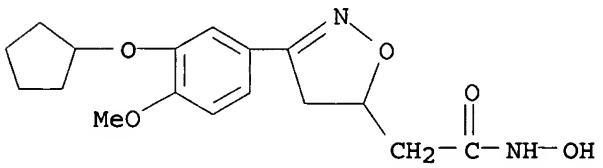


RN 167098-93-3 HCAPLUS
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172678-99-8 HCAPLUS
CN 5-Isoxazoleacetamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



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